PATENT
Atty. Docket No.: 17726A-000420

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Examiner: Unknown
Lee *et al. al.*.	Art Unit: Unknown
Application No.: Not assigned	COMMENTS OF LEE *et al.*
Filed: Herewith	
For: PRODUCTS AND METHODS FOR CONTROLLING THE SUPPRESSION OF THE NEOPLASTIC PHENOTYPE	

10028726.122101

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This paper is filed in connection with the Statement of Inventorship of Dr. Theodore Friedmann and Dr. Jiing-Kuan Yee.

Applicants inventorship investigation

In February, 2000, the assignee of the present application, the Regents of the University of California (the Regents), requested the undersigned to investigate whether Dr. Friedmann and others in his laboratory should be included as inventors on certain patent applications directed to the retinoblastoma gene and its uses. Dr. Friedmann had raised issues regarding inventorship for the use of the retinoblastoma (Rb) gene in gene therapy techniques. He did not contend that he was involved in the cloning of the gene itself, its use in diagnosis of disease, or the use of the Rb protein to treat disease. The only question addressed was the contributions of Dr. Friedmann and his lab to the use of the Rb gene in gene therapy.

To investigate this issue, Drs. Friedmann and Yee, two of the currently named inventors (Drs. Wen-Hwa Lee and Su Huang), as well as others were interviewed to understand the facts surrounding the conception and reduction to practice of the invention. No new contemporaneous evidence of conception or reduction to practice was provided. In the course of the

investigation, the attorney who filed the original applications, Bernard Kleinke, was also interviewed. Although Mr. Klienke did not remember the particular facts of this case, he indicated that it is his general practice to investigate inventorship in all applications he prepares and files.

The facts determined in the investigation are as follows. Dr. Lee and his colleagues cloned the Rb gene in 1987. The cloning and identification of the gene is reported in Lee *et al., Science* 235:1394 (1987). At some point in 1987, members of Dr. Lee's lab discussed with members of Dr. Friedmann's lab the use of retroviral vectors to introduce the cloned gene into cells lacking Rb function. This collaboration arose because Dr. Friedmann's lab had expertise in gene delivery arising from Dr. Friedmann's interest in gene therapy techniques. At the request of Dr. Lee, Dr. Yee prepared retroviral vectors comprising the Rb gene. According to Dr. Yee, these vectors were based on vectors previously used to express other genes in other cells. Dr. Yee prepared the constructs and introduced them into a packaging cell line to produce infectious viral particles. Dr. Huang then used the virus produced by the packaging cells to introduce the Rb gene into cancer cells that lacked Rb. This work was eventually published in Huang *et al. Science* 242:1563. Both Drs. Friedmann and Yee are authors on this paper.

The inventorship investigation focussed not on who performed the critical experiments, but who conceived of the use of the Rb gene for gene therapy. The inventorship investigation therefore revolved around whether the named inventors had conceived of the use of Rb to treat disease before the collaboration with Dr. Friedmann's lab or whether the idea was suggested by Dr. Friedmann or someone else in his lab.

Throughout the investigation, Dr. Lee maintained that use of the Rb gene for gene therapy was conceived before the collaboration with Dr. Friedmann. Dr. Friedmann, on the other hand, stated that the idea of using the gene in this way had come from him. As noted above, no new contemporaneous evidence of conception or reduction to practice was provided. The determination, however, took the following into consideration. Dr. Lee's lab was interested in cloning and characterizing the Rb gene, a gene related to an inherited form of cancer (retinoblastoma) and known to be inactivated in retinoblastoma cells. Dr. Friedmann's lab had expertise and interest in developing gene therapy techniques. At the time of the invention, however, the possibility that genes could be used to treat disease had been described in the literature. Thus, although Dr. Friedmann was clearly an expert in gene therapy, it is not inconceivable that the use of Rb in gene therapy occurred to the named inventors before the collaboration with Dr. Friedmann's lab.

Based on these facts, it was recommended that, in the absence of clear evidence that the determination made twelve years ago was incorrect, inventorship should not be changed.

Comments on Statement of Inventorship of Dr. Theodore Friedmann and Dr. Jiing-Kuan Yee

It is, of course, in the interest of all parties that the proper inventors be identified in this application. As noted above, the Regents investigated the contributions of Drs. Friedmann and Yee and found no new evidence upon which to change inventorship. Drs. Friedmann and Yee continue to assert, however, that the inventorship is incorrect and have presented voluminous evidence and argument to support that conclusion. Most of the evidence provided in the Statement of Inventorship is consistent with the facts uncovered in the Regents inventorship investigation and is not disputed. It should be noted, however, that the Statement apparently includes only facts and opinion obtained from Drs. Friedmann and Yee and does not reflect information obtained from the currently named inventors. The following points should be considered in evaluating this additional evidence.

It is the position of Drs. Friedmann and Yee that without conception of a vector capable of introducing the Rb gene into cancer cells, a complete conception of the invention was not possible (*see*, Statement of Inventorship page 2, first full paragraph). This argument is based on the assertion that introduction of nucleic acids into cells was not routine at the time of the invention. In particular, Drs. Friedmann and Yee argue in Section C of their Statement that the state of the art of retroviral vectors was such that delivering any particular gene to any particular cell type to produce any particular phenotype was not routine.[1]

As evidence of their position, Drs. Friedmann and Yee, cite Xu *et al. Virology* 171:331 (1989) (Friedmann Exhibit 10). The first sentence of this publication states: "Several effective and efficient methods have been developed for the introduction of foreign genetic information into mammalian and other eukaryotic cells." As argued in the Statement, the thrust of

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[1] It should be made clear that arguments regarding the difficulties of designing vectors and introducing nucleic acids into cells are the opinion of Drs Friedmann and Yee, alone. Since Drs. Friedmann and Yee are represented in this matter by separate counsel, nothing in these arguments should be construed in any way as applicants' admissions regarding the utility or enablement of any claims in this or related applications. To the extent the arguments presented in the Statement are inconsistent with arguments made by applicants or their representatives in this or related applications, they are expressly disavowed. Applicants strongly disagree with the implications of the arguments made by Drs. Friedmann and Yee. Since they are outside the scope of the present matter they will not be addressed further.

the paper appears to relate to the technical difficulties in developing guidelines for consistent production of stable and efficient vectors (*see*, block quote on page 14 of Statement). At best, this publication could be used to assert that problems remained in optimizing retroviruses for routine use in the production of animal models of disease or as gene therapy vectors. It does not show that introducing nucleic acids into cells to obtain a desired phenotype was beyond the level of ordinary skill in the art at the time of the invention.

Drs. Friedmann and Yee do not provide new contemporaneous evidence of the facts surrounding the conception of the present invention. Instead, they assert that it would be impossible to conceive of the invention in the absence of a particular vector. Their own evidence, however, establishes that "several effective and efficient methods" for delivering nucleic acids into mammalian cells were available at the time of the invention. These facts are consistent with the Regents' conclusion that, because methods for delivering nucleic acids into mammalian cells were available, it was possible for one of skill to conceive of a method of delivering Rb to cancer cells without conceiving of a particular vector by which this could be accomplished.

The Statement also provides extensive evidence of the expertise of Dr. Friedmann and his lab in the design and use of retroviral vectors.[2] These facts were also found in the Regents' investigation and are not disputed. The relative expertise of Drs. Lee and Friedmann, however, is not relevant to this inquiry. So long as those of skill recognized that there were several effective and efficient methods for introducing nucleic acids into cells, Dr. Friedmann's undisputed expertise is more relevant to reduction to practice than conception.

Drs. Friedmann and Yee point out that construction and design of the pLRbRNL vector was entirely the result of their efforts (*see*, Section V. B of the Statement). This fact was also found in the Regents investigation. Also consistent with the Regents investigation is that fact that the vector was made from a vector (pLRRNL) previously designed and used in Dr. Friedmann's lab. The Statement appears to argue, in addition, that the construction of pLRbRNL involved further judgment and expertise (*See*, paragraph bridging pages 22 and 23 of Statement). Although this could be the case, it should be noted that construction of the new vector was based on the replacement of the reporter gene, Lux, in pLRRNL with the Rb gene (*see*, Figure 1A of the present

application). It is difficult to see how this work required expertise beyond the ordinary skill in the art.

The statement of legal principles governing inventorship in the Statement are generally not disputed. Consistent with the Regents inventorship investigation, Drs. Friedmann and Yee emphasize that conception is the touchstone of inventorship. On pages 17 and 18, they cite *Hiztemann v. Rutter* 58 USPQ2d 1161 (Fed. Cir. 2001). This case relates to conception of an interference count directed to methods for producing recombinant hepatitis surface antigen particles having a sedimentation rate "virtually identical to authentic 22 nm hepatitis surface antigen particles" (*Id* at 1165). In that case, the court held that this language was a material limitation of the count (*Id.* at 1167) and that, in light of the state of the art, conception of the invention required a demonstration that, in fact, particles having these properties could be produced. *Id.* at 1167.

In citing this case, Drs. Friedmann and Lee apparently allege that conception of the methods claimed in the present application require a demonstration that, in fact, the proliferation of cancer cells can be suppressed using the Rb gene. Drs. Friedmann and Yee, however, do not allege that they performed the experiments in which the Rb gene was actually introduced into cells. As noted above, the Regents investigation determined that Dr. Su Huang performed these experiments. In the absence of evidence that Drs. Friedmann and Yee were involved in these experiments, reliance on the holding in *Hitzemann* does not appear to support the arguments presented in the Statement.

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[2] Dr. Lee, however, was not unfamiliar with retroviruses. As evidenced by the attached *cirriculum vitae*, Dr. Lee's graduate work focussed on retroviruses and he has published numerous articles in this area (*see*, Lee *et al.* Exhibit 1, references 1-9 in list of Publications and references 1-7 in list of Review Articles).

Conclusion

As noted above, Dr. Lee has maintained that introduction of Rb genes into cancer cells was conceived before his collaboration with Dr. Friedmann. Drs. Friedmann and Yee obviously disagree. Despite voluminous evidence provided with their Statement, Drs. Friedmann and Yee have not provided any contemporaneous evidence relevant to how this particular invention was conceived. In the absence of evidence relevant to the events that occurred in 1987 and 1988, arguments and evidence relating to the precise state of the art and the relative expertise of Drs. Lee and Friedmann tend to cloud rather than clarify this question. The Regents are clearly obligated to change inventorship in light of evidence of a mistake in the original inventorship determination. They have not, however, been made aware of evidence that, in their judgment, requires such a change. If the judgment of the USPTO is otherwise, inventorship will be changed accordingly.

Respectfully submitted,

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Exhibit 1

Curriculum Vitae

Wen-Hwa Lee

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University of Texas Health Science Center
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San Antonio, Texas 78245
Tel: 210-567-7351
Fax: 210-567-7377
Email: leew@uthscsa.edu

BIRTH DATE: June 1, 1950

CITIZENSHIP: USA

MARITAL STATUS: Married with two children

EDUCATION:

Ph.D. 1978 - 1981	Department of Molecular Biology University of California, Berkeley
M.S. 1975 - 1977	Institute of Biochemistry National Taiwan University
B.S. 1968 - 1972	Department of Biology National Taiwan Normal University

ACADEMIC APPOINTMENTS:

1996 - present	Chairman, Dept. of Molecular Medicine The University of Texas Health Science Center at San Antonio
1991 - present	Alice P. McDermott Distinguished University Chair Director, Institute of Biotechnology The University of Texas Health Science Center at San Antonio
1991 - present	Professor, Department of Pathology The University of Texas Health Science Center at San Antonio
1993 - 1997	Chair, Graduate Program of Molecular Medicine The University of Texas Health Science Center at San Antonio
1991 - 1994	Adjunct Professor, Chinese University of Science and Technology, Hefei, China
1990 - 1991	Professor, University of California, San Diego
1987 - 1990	Associate Professor, University of California, San Diego

1987 - 1988	Visiting Professor, Institute of Molecular Biology Sinica Academia, Taipei, Taiwan
1984 - 1987	Assistant Professor, University of California, San Diego
1983 - 1984	Visiting Scientist, Lawrence Berkeley Laboratory
1982 - 1983	Research Scientist, Cetus Corporation, Berkeley
1981 - 1982	Postdoctoral Fellow, University of California, Berkeley
1977 - 1978	Teaching Assistant, Institute of Biochemistry National Taiwan University, Taipei
1973 - 1975	Military Service (Junior Lieutenant), Taiwan, ROC
1972 - 1973	Teacher-Nankung Middle School-Taipei

HONORS:

2001	Presidential Award, Society of Chinese Bioscientists in America
1999	F.E. Shideman-Sterling Award, University of Minnesota
1999	Li Shih-Chen Distinguished Lectureship, University of Pittsburgh
1994	Elected Member, Academia Sinica, Republic of China
1994	Alcon Research Award
1994	Travelship from the U.S. National Committee for the International Union Against Cancer (UICC)
1992	Outstanding Scientific Achievement award, Society of Chinese Bioscientists in America.
1991	Alice P. McDermott Distinguished University Chair, University of TX
1991	National Institute of Health Director lectureship
1977	Graduate scholarship of the Ministry of Education
1976	Graduate scholarship of the Ministry of Education
1972	Mr. Yuen-Wu Wang's scholarship (for top student in the college)
1971	Natural Science Award
1970	Natural Science Award (for top student in the Department)

MEMBERSHIPS:

International Association for Comparative Research on
Leukemia and Related Diseases
American Society for Microbiology
American Association for the Advancement of Science
New York Academia of Science
The Association for Research in Vision and Ophthalmology
Society of Chinese Bioscientists in America
American Associate of Cancer Research (AACR)
American Society of Human Genetics

EDITORIAL BOARD:

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Journal of Biomedical Science
inScight Editorial Board
The Women's Oncology Review
Cancer Research (Associate Editor)

ADVISORY BOARD:

Member, Institute of Biological Chemistry, Academia Sinica (Nov., 2001 – Aug., 2004)
Member, Bioenterprise Steering Advisory Committee, Ministry of Economic Affairs, Development Center for Biotechnology, Taiwan (2001 – Present)
Member, Scientific Council for Foundation for Cancer Gene Therapy (2001 – Present)
Member, Board of International Scientific Advisers, SHARF Foundation (2001 - Present)
Member Board of Scientific Advisors, Cancer Institute of Chinese University of Hong Kong (1994 - Present)
Member, Advisory Committee for Biotechnology & Pharmaceutical Industries Program Office (MOEA), R.O.C. (1998 - Present)
Member, Advisory Committee, Institute of Biomedical Sciences, Academia Sinica (1997 – Present)
Scientific Advisory Board, World Scientific Publishing Company, Inc. (1995 - Present)
Scientific Council of the National Health Research Institutes, Taipei, Taiwan (1997 - Present)
Chairman of Cancer Review Panel, National Health Research Institutes, Taipei, Taiwan (1999 – Present)
Member, Search Committee for Director, Institute for Drug Development (1999 – 2001)
Member, Advisory Committee, Children's Cancer Research Center, UTHSC-SA (1999 – 2000)
Member, Board of Directors, Cancer Therapy and Research Center, San Antonio, TX (1999 – 2000)
Scientific Advisor for Search Committee for Cancer Genetics Director, Arthur G. James Cancer Hospital and Research Institute, Columbus, Ohio (1994)
Chairman, Scientific Advisory Board of Canji, Inc. (1990 - 1995)
Member, Scientific Advisory Board of Canji Research Institute, Schering Plough (1996 - 1999)
Member, Recruitment and Advisory Committee, National Health Research Institutes, Taiwan, R.O.C. (1996 - 1998)

SERVICE:

Chair, Selecting Committee for Life Science, Presidential Science Award, Republic of China (2001 – Present)
Member, NCI Cancer Center Review Subcommittee A (1998 – Present)
Member, Executive Committee, San Antonio Cancer Institute (1997 – Present)
Program Director for Tumor Suppressor Gene & DNA Repair, San Antonio Cancer Institute (1997 – Present)
Director, Training Program for Breast Cancer (1994 - Present)
Building Planning Committee for UTHSCSA (1996 – 1999)
Ad hoc Committee Member for American Cancer Society Research Professorship (1994)

Member of National Institute of Health - Cell Biology & Physiology Study Section II (1992 - 1996)
Organizer, Texas Triangle Meeting for Molecular Medicine (1992, 1993, 1994 & 1995)
Member of Committee for the University Distinguished Lecture Series, UTHSC-SA, (1995)
Member of Dual Degree Programs Committee, UTHSCSA (1995 - 1996)
Member of the Graduate School Strategic Planning Committee, UTHSCSA (1992 - 1996)
Member of Core Committee in Molecular Pathology, Ph.D. Program and Admission Committee for Graduate Student, UCSD (1984 - 1991)
Chair of Examination Committee, UCSD (1984 - 1991)
Member of National Institute of Health - Visual Science Study Section Adhoc Committee (1990)
Director of Training Program of Molecular Genetics of Vision Research (1989 - 1991)
Director, Research Program of Cancer Suppression by the Retinoblastoma Gene (1989 - 1991)
Member of University of California, Cancer Research Coordinating Committee (1990 - 1991)
Councilor for Society of Chinese Bioscientists in America (SCBA) - (1996-1999)
Member, Breast Cancer Progress Review Group, National Cancer Institute (1997)
Member, Research Fellowship Committee, American Association for Cancer Research, Inc. (AACR) - (1998)

PATENTS:

1. U.S. Patent #4,942,123, July 17, 1990, ppRB110-Phosphoprotein-The Retinoblastoma Susceptibility Gene Product, **Lee W-H** and Lee E Y-HP.
2. U.S. Patent #5,011,773, April 30, 1991, Human Esterase D, Its Uses and a Process of Purification, **Lee W-H** and Lee E Y-HP.
3. U.S. Patent #5,532,220, July 2, 1996, Genetic Mechanisms of Tumor Suppression, **Lee W-H** and Chen P-L.
4. European Patent #EP 0 440 744 B1, October 12, 1997, Products and Methods for Controlling the Suppression of the Neoplastic Phenotype, **Lee W-H**, Huang, Huei-Jen, Su, and Lee, Eva Y.,H.,P.
5. U.S. Patent #5,821,070, October 13, 1998, Antibodies Reactive with Retinoblastoma Binding Proteins and Methods of Using Same, **Lee W-H** and Shan B.
6. U.S. Patent #5,851,991, December 22, 1998, Therapeutic Use of the Retinoblastoma Susceptibility Gene Product, **Lee W-H**, Lee E Y-HP, Goodrich DW, Shepard HM, Wang NP, and Johnson D.
7. U.S. Patent #5,858,771, January 12, 1999, Products and Methods for Controlling the Suppression of the Neoplastic Phenotype, **Lee W-H**, Huang H-JS, and Lee EY-H.P.
8. U.S. Patent #5,998,134, December 7, 1999, Retinoblastoma Gene-Cancer Suppressor and Regulator, **Lee W-H** and Lee E Y-HP.
9. New Zealand Patent No. 333635 based on PCT/US97/11946 and U.S. Serial No. 60/015,863, BRCA1 Compositions and Methods for the Diagnosis and Treatment of Breast Cancer, **Lee W-H**, et al.
10. U.S. Patent #6,051,396, April 18, 2000, Method for producing retinoblastoma gene protein products, **Lee W-H** and Lee E Y-HP.

PUBLICATIONS:

Dr. Wen-Hwa Lee's publications are primarily in the areas of molecular cancer genetics, mainly specializing in the mechanism of tumor suppressor genes and oncogenes functions, cancer gene therapy and cancer progression. His publications include more than a hundred original research articles and forty invited articles in journals such as Science, Nature, Cell, Proc. Natl. Acad. Sci, Genes & Dev. EMBO J etc.

The following is a list of the full-length refereed publications.

1. **Lee W-H**, Bister K, Pawson A, Robins T, Moscovici C and Duesberg PH: Fujinami Sarcoma Virus: An Avian RNA Tumor Virus with a Unique Transforming Gene. **Proc. Natl. Acad. Sci.**, 77: 2018-2022 (1980).
2. Bister K, **Lee W-H** and Duesberg PH: Phosphorylation of the Nonstructural Proteins Encoded by Three Avian Acute Leukemia Viruses and by Avian Fujinami Sarcoma Virus. **J. Virol.**, 36: 617-621 (1980).
3. Martin GS, **Lee W-H** and Duesberg PH: Generation of Nondefective Rous Sarcoma Virus by Recombination between Deletion Mutants. **J. Virol.**, 36: 591-594 (1980).
4. **Lee W-H**, Bister K, Moscovici C and Duesberg PH: Temperature-sensitive Mutants of Fujinami Sarcoma Virus: Tumorigenicity and Reversible Phosphorylation of the Transforming p140 Protein. **J. Virol.**, 38: 1064-1076 (1981).
5. **Lee W-H**, Nunn M and Duesberg PH: The src Genes of 10 Rous Sarcoma Virus Strains, Including Two reportedly Transduced from the Cell are Completely Allelic; Putative Markers of Transduction are not Detected. **J. Virol.**, 39: 758-776 (1981).
6. **Lee W-H**, Liu C-P and Duesberg PH: DNA Clone of Avian Fujinami Sarcoma Virus with Temperature-Sensitive Transforming Function in Mammalian Cells. **J. Virol.**, 44: 401-412 (1982).
7. **Lee W-H**, Phares W and Duesberg PH: Structure Relationship Between Chicken DNA locus, proto *fps*, and transforming Gene of Fujinami Sarcoma Virus, gag-*gps*. **Virology**, 129: 79-93 (1983).
8. Duesberg PH, Phares W, and **Lee W-H**: The low Tumorigenic Potential of PRC II, among viruses of the Fujinami Sarcoma Virus Subgroup, Corresponds to an internal (fps) Deletion of the Transforming Gene. **Virology**, 131: 144-158 (1983).
9. Seeburg P, **Lee W-H**, Nunn M and Duesberg PH: The '5 ends of the transforming gene of Fujinami sarcoma virus and of the cellular proto-*fps* gene are not colinear. **Virology**, 133: 460-463 (1984).
10. **Lee W-H**, Murphree AL and Benedict WF: Expression and Amplification of N-*myc* Gene in Primary Retinoblastoma. **Nature** (London), 309:458-460 (1984).
11. Lee EY-HP, **Lee W-H**, Kaetzel C, Parry G and Bissell MJ: Interaction of Mouse Mammary Epithelial Cells with Collagenous Substrata: Regulation of casein gene expression and secretion. **Proc. Natl. Acad. Sci.**, 82: 1419-1423 (1985).
12. Lee EY-HP, and **Lee W-H**: Molecular Cloning of the Human Esterase D Gene, A Genetic Marker of Retinoblastoma. **Proc. Natl. Acad. Sci.**, 83: 6337-6341 (1986).
13. **Lee W-H**, Wheatley W, Benedict WF, Huang C-M, and Lee EY-HP: Purification, biochemical characterization, and biological function of human esterase D. **Proc. Natl. Acad. Sci.**, 83: 6790-6794 (1986).
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16. **Lee W-H**, Bookstein R, Wheatley W, Benedict WF and Lee EY-HP: A null allele of esterase D is a marker for genetic events in retinoblastoma formation. **Human Genetics**, 76: 33-36 (1987).
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24. **Lee W-H**, Bookstein R and Lee EY-HP: Studies on the Human Retinoblastoma Susceptibility Gene. **J. Cell. Biochem.**, 38: 213-227 (1988).
25. Huang H-JS, Yee J-K, Shew J-Y, Chen P-L, Bookstein R, Friedmann T, Lee EY-HP and **Lee W-H**: Suppression of the Neoplastic Phenotype by Replacement of the RB Gene in Human Cancer Cells. **Science**, 242: 1563-1566 (1988).
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29. Bookstein R, Lee EY-HP, Peccei A and **Lee W-H**: Human Retinoblastoma Gene: Long-Range Mapping and Analysis of Its Deletion in a Breast Cancer Cell Line. **Mol. & Cell. Biol.**, 9 (4): 1628-1634 (1989).
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(B) **Review articles (W.-H. Lee):**

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INVITED SPEAKER (Following are notable from more than 200 talks):

1. Karolinska Institute, Sweden, August 1987.
2. Imperial Cancer Research Institute, London, August 1987.
3. National Institute of Health, Sept. 1987.
4. UCLA Symposia on Molecular & Cellular Biology, Keystone, CO, Jan. 1988.
5. Cold Spring Harbor Laboratory, New York, June 1988.
6. Gordon Research Conference - Peptide Growth Factors
   Discussion Leader - August 1988.
7. Genetics Research Colloquium, Stanford University, October 1988
8. Yale University, Department of Biology, December 1988.
9. Cold Spring Harbor Banbury Meeting, New York, March 29 - April 1, 1989.
10. Aspen Cancer Conference, Aspen, Colorado, July 1989.
11. Molecular Genetics Gordon Conference, Rhode Island, August 1989.
12. The 20th Symposium of the Princess Takamatsu Cancer Research Fund, Tokyo, Japan, Nov. 1989.
13. Department of Molecular and Cellular Biology, University of California, Berkeley, February 20, 1990.
14. UCLA Symposium, Taos, New Mexico, March 3-9, 1990.
15. 31st Annual Meeting of British Cancer Association, March 19-22, 1990.
16. The 3rd Kyoto International Symposium on Medical Sciences, Kyoto, Japan, June 15-18, 1990.
17. The 6th International Conferences on Differentiation and Neoplastic Cells, Vancouver, Canada, July 29 - August 2, 1990.
18. Gordon Research Conference on Peptide Growth Factors, Rhode Island,

Aug. 6-10 1990, Session Chair.

19. Gordon Research Conference on Cancer, Rhode Island, Aug. 12-17 1990, Session Chair.
20. Cold Spring Harbor Symposium on Origins of Human Cancer, Sept. 4 - 10, 1990.
21. Dept. of Biology, John Hopkins University, Oct.18, 1990.
22. U.S. - Japan Exchange Program Seminar on "Molecular Mechanisms in Oncogenesis and Tumor Progression", Kauai, Hawaii, January 17, 18,1991.
23. University of Wisconsin Clinical Cancer Center, Madison, Wisconsin, January 30, 1991.
24. "Lineberger Cancer Research Center Seminar Series", University of North Carolina, Research Triangle, North Carolina, March 12, 1991.
25. National Institute of Health Lecture, Bethesda, Maryland, May 23, 1991.
26. Cold Spring Harbor Laboratory Symposium on "Cell Cycle", May 29 - June 5, 1991.
27. Seventh Nagoya International Symposium on Cancer Treatment, Nagoya, Japan, September 29-30, 1991.
28. Forty-Fourth Annual Symposium on Fundamental Cancer Research - Genetic Mechanisms of Cancer, M.D. Anderson Cancer Center, Houston, Texas, October 29,-November 1, 1991.
29. Maimonides Cancer Research Conference, Ein-Gedi, Israel, November 25 - 30, 1991.
30. Keystone Symposium "Negative Growth Control", Keystone, Colorado, January 25 - February 2, 1992.
31. Challenges and Controversies in Cancer Research, University of Ohio, Columbus, September 8, 1992.
32. The Legacy of Cell Fusion, Henry Harris Symposium, Oxford England, September 24, 1992.
33. "Keystone Symposia on Molecular and Cellular Biology, Keystone, Colorado, January 17-24, 1993.
34. AACR conference, "Oncogenes and Antioncogenes in Differentiation, Development, and Human Cancer", Big Sky, Montana, February 1-6, 1993.
35. Stanford University, The Department of Pharmacology, Stanford, CA, February 24, 1993.
36. Harvard Medical School, The Department of Microbiology, Boston, MA, March 2, 1993.
37. Comprehensive Cancer Center, The University of Michigan, Ann Arbor, MI, March 12, 1993.
38. American Association for Cancer Research, "Genetic Control of Cell Growth", April 13-17, 1993, Galveston, Texas.
39. 46th Annual Symposium on Fundamental Cancer Research "Mechanisms for Cell Growth and Differentiation, M.D. Anderson Cancer Center, Houston, TX, October 12-15, 1993.
40. Session Chair, "Keystone Symposia on Tumor Suppressor Genes, Taos, New Mexico, January 17-24, 1994.
41. 28th annual meeting European Society for clinical investigation, April, 1994 Toledo, Spain
42. 20th Annual ICSABER Graduate Research Forum, Ohio State University, May, 1994
43. 59th Symposium on Quantitative Biology: Molecular Genetics of Cancer, June 1994. Cold Spring Harbor Laboratory
44. Summer Mini-symposium, "Cell Cycle Regulation", Frederick, Maryland, July, 1994

45. Seminar for Lawrence Berkeley Laboratory and the University of California, Berkeley, August, 1994.
46. "Modern Developments in Cancer Therapeutics" AACR/IBS Special Conference in Taipei, November, 1994.
47. Plenary speaker at 17th Annual San Antonio Breast Cancer Symposium, December, 1994.
48. Distinguished Lecture Series at The Cancer Institute of New Jersey, Piscataway, New Jersey, April, 1995.
49. Seminar at Fred Hutchinson Cancer Research Center, Seattle, Washington, June, 1995.
50. Plenary lecture and session chair at the Sixth International Symposium of the Society of Chinese Bioscientists in America (SCBA), Vancouver, Canada, June, 1995.
51. "Cancer: The Interface between Basic and Applied Research", AACR Special Conference, Baltimore, Maryland, November, 1995.
52. Keynote speaker, "Fifth International Symposium on Cancer", Cancer Research Center, Seoul National University College of Medicine, Korea, March, 1996.
53. Genetics Seminar Program, Yale School of Medicine, New Haven, Connecticut, April, 1996.
54. Conference of the General Motors Cancer Research Foundation, "Origins of Breast and Prostate Cancer", Bethesda, Maryland, June, 1996.
55. Plenary speaker, The Second International Symposium and Workshop of Asia Pacific Society of Bioscientists, Hong Kong University of Science & Technology, Clear Water Bay, Hong Kong, July, 1996.
56. Keynote speaker, National Health Research Institutes Symposium on Cancer, Tao-Yuan, Taiwan, August, 1996.
57. Schweppe Colloquium, Northwestern University Medical Center, Chicago, Illinois, October, 1996.
58. 1997 Keystone Symposia meeting entitled, "Genetics of Human Cancer: Pathogenesis and Diagnosis", January, 1997.
59. AACR Special Conference in Cancer Research, entitled "Basic and Clinical Aspects of Cancer Research", Keystone, Colorado, March, 1997.
60. Cambridge Symposia conference on "Genetic Approaches to Breast and Prostate Cancer," Lake Tahoe, California, March, 1997.
61. Gordon Research Conference on Mammary Gland Biology, Plymouth State College, Plymouth, New Hampshire, June, 1997.
62. Breakthrough Breast Cancer, First International Workshop on the Function of BRCA1 and BRCA2, Churchill College, Cambridge University, United Kingdom, September, 1997.
63. Keynote speaker, Sixth Symposium of The Chinese Society of Molecular and Cellular Biology, Taiwan, February, 1998.
64. Keynote speaker, The Society for Chinese Bioscientists in America (SCBA) Texas Chapter 1998 Symposium, UTMB Galveston, April, 1998.
65. Section Chairperson, International Symposium on "The worldwide herbal industry: present and future," Hong Kong, P.R.C., July, 1998.
66. International Conference on Gene Targets for Cancer Treatment, Capri, Italy, September, 1998.
67. Organizer and session chair at the New York Academy of Sciences Conference, "Anti-Cancer Proteins and Drugs: Structure, Function, and Design," New York City, New York, November, 1998.
68. Li Shih-Chen Distinguished Lectureship, University of Pittsburgh, February, 1999.

69. 1999 Gordon Conference on Cancer, Salve Regina University, Newport, R.I., August, 1999.
70. Session Chair, 8th International Symposium of SCBA, Hong Kong, China, August, 1999.
71. AACR Special Conference, "Genetic and Functional Consequences of Cell Cycle Alteration in Cancer," San Diego, CA, October, 1999.
72. F.E. Shideman Sterling Lectureship, Department of Pharmacology, University of Minnesota, October, 1999.
73. Biotechnology & Scientific Workshop, sponsored by US-ROC (Taiwan) Business Council, San Antonio, TX, November, 1999.
74. Keynote speaker, Association of American Chinese Professionals Foundation 1999 Winter Conference, San Antonio, TX, November, 1999.
75. University of North Carolina Lineberger Comprehensive Cancer Center Seminar Series, March, 2000.
76. Annual meeting of the Environmental Mutagen Society, New Orleans, LA, April, 2000.
77. University of California at Irvine, April, 2000.
78. NCI Breast Cancer Think Tank Retreat 2000, Chantilly, VA, July, 2000.
79. University of Mississippi Medical Center Symposium, Southeastern Pharmacology Society Meeting, August, 2000.
80. Plenary Lecture, Second Brook Top Symposium, Taiwan Society for Biochemistry and Molecular Biology, Taipei, Taiwan, November, 2000.
81. National Taiwan University, College of Medicine, Taipei, Taiwan, November, 2000.
82. National Tsing Hua University, Taipei, Taiwan, November, 2000.
83. National Yang Ming University, Taipei, Taiwan, January, 2001.
84. Advanced Studies Institute on the "Molecular Genetic Basis of Cancer", Hong Kong University of Science & Technology, Hong Kong, China, January, 2001.
85. Wistar Institute, Philadelphia, PA, February, 2001.
86. NCI Workshop, "BRCA1: Function in Cell Growth and Tumorigenesis," Rockville, MD, April, 2001.
87. 9th Symposium of Society of Chinese Bioscientist of America, Aug. 5, 2001, Taipei. Awardee Lecture " Cancer and genomic instability"

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.:
LEE *et al.*	Art Unit: To be assigned
Appl. No. To be assigned	Examiner: To be assigned
Filed: Herewith	Atty. Docket: 17726A-000420
For: **Process and Methods for Controlling the Suppression of the Neoplastic Phenotype**	

Rebuttal to Comments of Lee *et al.* Regarding the Statement of Inventorship of Dr. Friedmann and Dr. Yee

Commissioner for Patents
Washington, D.C. 20231

Sir:

In reply to the Comments of Lee *et al.* filed by the assignee of the present application, The Regents of the University of California, with respect to the Statement of Inventorship filed by Dr. Friedmann and Dr. Yee, Drs. Friedmann and Yee submit these further remarks.

It is important to note that The Regents of the University of California have confirmed that the factual assertions presented in the Declarations of Dr. Yee and Dr. Friedmann and in the Statement of Inventorship are not disputed. Indeed, the Regents state: "[m]ost of the evidence provided in the Statement of Inventorship is consistent with the facts uncovered in the Regents inventorship investigation and is not disputed." (*See* Comments of Lee et al. at page 3, lines 8-10.) Thus, the Regents do not dispute that Dr. Friedmann and his lab had extensive expertise in the design and use of retroviral vectors in human gene therapy in the late Summer-Fall of 1987. (*See, e.g.,* Comments of Lee et al. at page 4, lines15-17.) Nor do the Regents

dispute that the conception of a design for and construction of the pLRbRNL vector, which was the same and only vector used to introduce the human retinoblastoma susceptibility gene (Rb) into tumor cells to demonstrate for the first time the suppression of the neoplastic phenotype by a single tumor suppressor gene, was "entirely" the result of the efforts of Drs. Friedmann and Yee. (*See* Comments of Lee et al. at page 4, lines 21-23.)

Rather, it is the position of the Regents that the undisputed contributions of Drs. Friedmann and Yee to conception of the means for carrying out the claimed methods of gene therapy do not amount to joint conception of the claimed invention. Indeed, it is the Regents' position that conception of the claimed methods of gene therapy was complete once the general idea of introducing the Rb gene into cancer cells was conceived, and that conception of the actual steps of a specific, operative means for achieving that objective is immaterial. But as discussed in detail in the Statement of Inventorship, the Regent's position is directly contrary to the established law on this issue.

The present claims are directed to methods of gene therapy. More specifically, the claims are broadly directed to methods of therapeutically treating inactive, mutative or absent cancer suppressing genes comprising contacting said inactive, mutative or absent cancer suppressing genes with at least a portion of intact cancer suppressing genes (i.e. Rb). (*See*, *e.g.*, claims 41 and 43 of the present application).

The Federal Circuit's predecessor, the Court of Customs and Patent Appeals, has defined conception of an inventive process as follows:

> Conception of an inventive process involves proof of ***mental possession of the steps of an operative process*** and, if necessary, of ***means to carry it out*** to such a degree that nothing remains but routine skill for effectuation thereof. If after the claimed conception date extensive research was found necessary before achieving minimum satisfactory performance obviously the mental embodiment of that date was a mere hope or expectation, a statement of a problem, but not an inventive contribution.

(*Meitzner and Oline v. Corte and Meyer*, 161 USPQ 599, 603 (CCPA 1969), quoting *Alpert v. Slatin*, 134 USPQ 296 (CCPA 1962) (emphasis added)) (*See* Exhibits 11 and 12 to the Statement of Inventorship of Dr. Theodore Friedmann and Dr. Jiing-Kuan Yee). The Federal Circuit endorsed this rule very recently in *Hitzemann v. Rutter*, 58 USPQ2d 1161 (Fed. Cir. 2001). (*See* Exhibit 13 to the Statement of Inventorship) In that case, an interference case, the Federal Circuit ruled that Hitzemann's mere "hope" of obtaining hepatitis B surface antigen particles having the particle size and sedimentation rate limitations of the count at issue was insufficient to establish complete conception of the count, despite the fact that the hope was later realized. *Id.* at 1168.

The present case is analogous. It is clear that at the time Dr. Lee's group sought to collaborate with Dr. Friedmann's group on the Rb vector project, Dr. Lee, at the very least, did not have a definite and permanent idea of specific "means to carry out" his wish of providing expression of the Rb gene in osteosarcoma cells, and he had no idea whether or not

such expression would suppress the neoplastic phenotype (since it had never before been accomplished with a single gene). Thus, at the time that Dr. Lee sought the assistance of Dr. Friedmann's lab in designing a vector for introducing the Rb gene into osteosarcoma cells, Dr. Lee had no more than a wish or hope to achieve tumor suppression by gene therapy, but he did not have a conception of a complete and operative method for accomplishing it.

In their Comments, Applicants take a single statement from the Xu article (Exhibit 10 to the Statement of Inventorship) and cite it out of context as support for their contention that the conception of a design for and construction of the pLRbRNL vector was routine. On the contrary, a careful reading of the Xu article supports the assertions that Drs. Friedmann and Yee made in their Declarations, *i.e.*, that it would not have been possible in 1987 for someone to routinely reduce to practice a retroviral vector design for gene therapy, because there was no established "practice" at that time for designing and constructing stable and efficiently expressing vectors. (*See* Statement of Inventorship at pages 13-15.)

It is ironic that Dr. Lee now seeks to downplay the contributions of Drs. Yee and Friedmann as mere "pairs of hands" involved in routine reduction to practice of Dr. Lee's conception, since Dr. Lee has repeatedly emphasized the critical importance of those same contributions in his efforts to overcome an enablement rejection during prosecution of a parent application before the U.S. Patent and Trademark Office, and in his efforts to secure further funding for his research from the U.S. Government. Indeed, Applicants specifically cited the success of pLRbRNL in arguing that "*the Specification sets forth in clear and concise terms*

a method sufficient to enable the ordinarily skilled artisan to administer the RB gene in a vector to treat cancer." (*See* Statement of Inventorship at pages 28-29 (citing Exhibit 6)). Likewise, Dr. Lee touted the expertise and experience of the Friedmann in the grant application that he submitted to the National Cancer Institute shortly after the development of the pLRbRNL vector. (*See* Statement of Inventorship at pages 25-26 (citing Exhibit 8)). These prior statements against interest clearly contradict the Applicants' present, self-serving assertions that Drs. Yee and Friedmann acted essentially as mere "pairs of hands" for Dr. Lee.

In summary, it is undisputed that Dr. Friedmann and Dr. Yee conceived of the design for and constructed the specific retroviral vector disclosed in the application that was ultimately used to deliver the Rb gene to cancer cells and to demonstrate, for the first time ever, the suppression of the neoplastic phenotype by a single gene. The contribution of Drs. Friedmann and Yee amounted to joint conception of the claimed methods, because without conception of a vector capable of introducing the Rb gene into cancer cells, conception of the claimed methods of suppressing the neoplastic phenotype was not enabled and, therefore, incomplete.

Prosecution of the present application is an appropriate forum for the USPTO to act on this inventorship issue. *See, e.g., In re Reuter*, 210 USPQ 249, 255 (CCPA 1981) ("Evidence [of inventorship] submitted in a reissue protest proceeding should be considered on the same basis as other *ex parte* evidence. . . . Indeed, evidence produced during an *inter partes* proceeding can be more reliable and complete than that produced in an *ex parte* proceeding due to its adversary nature."). Accordingly, it is requested that the Examiner either

(1) issue a formal statement that the inventorship of the above-captioned application as filed is improper, and that Dr. Yee and/or Dr. Friedmann should be added as inventors; and/or (2) reject one or more claims under 35 U.S.C. § 102(f) on the ground of derivation due to the fact that Dr. Yee and/or Dr. Friedmann are coinventors of the subject matter of one or more claims of the above-captioned application yet have not been added as inventors.

Respectfully submitted,

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for Jorge A. Goldstein
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Date: 12/18/01

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.:
LEE *et al.*	Art Unit: To be assigned
Appl. No. To be assigned	Examiner: To be assigned
Filed: Herewith	Atty. Docket:
For: **Process and Methods for Controlling the Suppression of the Neoplastic Phenotype**	

Statement of Inventorship of Dr. Theodore Friedmann and Dr. Jiing-Kuan Yee

Commissioner for Patents
Washington, D.C. 20231

Sir:

I. Overview

Dr. Theodore Friedmann and Dr. Jiing-Kuan Yee assert that they are coinventors of certain subject matter disclosed and claimed in the above-captioned patent application (filed herewith). The current Applicants dispute this. In order to resolve this inventorship dispute in a fair and impartial manner, the assignee of the above-captioned application, The Regents of the University of California, has agreed to allow Dr. Friedmann and Dr. Yee to submit this Statement of Inventorship in conjunction with the above-captioned application, and to request and permit an impartial third party, the U.S. Patent and Trademark Office, to take action on the inventorship issue.

The claimed invention is directed to products and methods for the therapeutic and prophylactic treatment of mammals, and to methods for controlling the phenotypic expression of cancer due to the loss of tumor suppressor gene expression. More specifically, the application is directed to the suppression of the neoplastic phenotype in cancer cells by delivery of the human retinoblastoma susceptibility gene ("Rb") to said cells. It is undisputed that Dr. Friedmann and Dr. Yee conceived of the design for and constructed the specific retroviral vector disclosed in the application that was ultimately used to deliver the Rb gene to cancer cells. It is our position that the contribution of Drs. Friedmann and Yee amounted to joint conception of the claimed methods, because without conception of a vector capable of introducing the Rb gene into cancer cells, conception of the claimed methods of suppressing the neoplastic phenotype was not enabled and, therefore, incomplete.

II. Statement of Precise Nature of Relief Sought

Provided below are a description of the factual background of the collaboration that precipitated this inventorship dispute, and the controlling legal principles governing joint conception and conception of a claimed method or process. It is respectfully submitted that when the facts are properly considered in the framework of the controlling legal principles, it is clear that Dr. Friedmann and Dr. Yee are coinventors of certain subject matter claimed in the present application. Accordingly, it is requested that the Examiner either (1) issue a formal statement that the inventorship of the above-captioned application as filed is improper, and that Dr. Yee and/or Dr. Friedmann should be added as inventors; or (2) reject one or more claims

under 35 U.S.C. § 102(f) on the ground of derivation due to the fact that Dr. Yee and/or Dr. Friedmann are coinventors of the subject matter of one or more claims of the above-captioned application yet have not been listed as inventors.

III. Statement of Material Facts

It is submitted that the material facts at issue in this inventorship dispute are, for the most part, not contested. Rather, the dispute is the result of a disagreement as to whether Dr. Friedmann's and Dr. Yee's undisputed contributions to the conception of the claimed invention constitute inventorship.

A. The Claimed Invention

The disclosure of the present application, including the claims, is identical to that of U.S. Patent Application No. 08/337,855, which was filed on November 14, 1994, and named as inventors Wen-Hwa Lee, Huei-Jen Su Huang, and Eva Y. H. P. Lee. The application as filed relates generally to products and methods for the therapeutic and prophylactic treatment of mammals and to control the phenotypic expression of cancer. As filed, the application contains 47 claims, of which claims 41 and 43 are representative:

> 41. A method of therapeutically treating inactive, mutative or absent cancer suppressing genes comprising:
>
> treating said inactive, mutative or absent cancer suppressing genes with at least a portion of intact cancer suppressing genes.

> 43. A method of claim 41, wherein said treating includes: treating said inactive, mutative or absent cancer suppressing gene with a substance selected from the group consisting of an RB gene, a portion of said gene, or a mixture thereof.

The application makes clear that by RB is meant the human retinoblastoma susceptibility gene. (*See* page 18, line 17.) Indeed, the *only* disclosure in the application of experiments in which an inactive, mutative or absent cancer suppressor gene was treated with an intact form of said gene to successfully suppress the neoplastic phenotype in cells involved experiments in which the retinoblastoma gene was introduced into osteosarcoma cell line Saos-2 using a retroviral vector. (*See* pages 73-95.)

B. The Factual Background

1. The Collaboration Between the Lee and Friedmann Labs

Dr. Theodore Friedmann is currently Professor of Pediatrics and Director of the Human Gene Therapy Program at the Center for Molecular Genetics, School of Medicine, University of California at San Diego in La Jolla, California ("UCSD"). (*See* Declaration Under 37 C.F.R. § 1.132 of Theodore Friedmann, M.D., M.A. (Exhibit 1, attached) at ¶ 1.) Dr. Friedmann is recognized as one of the world's leading experts on human gene therapy. His 1972 article, "Gene therapy for human genetic disease," is considered to be a seminal paper on the topic. (*See* Exhibit 1 at ¶ 2.) Since 1998, he has served as a member of the Recombinant DNA Advisory Committee of the National Institutes of Health, which is charged with

evaluating all gene therapy protocols submitted to the Federal Government. He was recently appointed Chair of that Committee, a position that he will assume in December of 2001. (*See* Exhibit 1 at ¶ 2.)

Dr. Jiing-Kuan Yee is currently Associate Professor of Virology at the Beckman Research Institute of City of Hope National Medical Center in Duarte, California. (*See* Declaration Under 37 C.F.R. § 1.132 of Jiing-Kuan Yee, Ph.D. (Exhibit 2, attached) at ¶ 1.)

In 1987 and 1988, Dr. Friedmann's research group at the Center for Molecular Genetics, of which Dr. Yee was a member, was widely considered to be one of the world's foremost groups in terms of expertise and success with retroviral mediated gene transfer techniques and its applications to human gene therapy. (*See* Exhibit 1 at ¶ 3; Exhibit 2 at ¶ 3.) In about the late Summer or Early fall of 1987, Dr. Friedmann's group was approached by Dr. Wen-Hwa Lee's research group about the possibility of constructing a vector for introducing the human retinoblastoma susceptibility gene ("Rb") into cancer cells. At the time, Dr. Wen-Hwa Lee headed a research group in the Department of Pathology of the Center for Molecular Genetics at UCSD. Earlier that year, Dr. Lee's group had published a paper describing the cloning, identification and sequence of the Rb gene. Furthermore, there was at that time an existing collaboration between the Lee laboratory and the Friedmann laboratory to characterize the structure of the Rb gene. Results of those studies were published jointly by the Friedmann and Lee laboratories in 1988. (*See* Exhibit 1 at ¶ 4; Exhibit 2 at ¶ 4.)

Dr. Yee was friends with several members of Dr. Lee's research group at that time, including Huei-Jen Su Huang, and they frequently discussed generally the various projects on which their respective labs were working. Likewise, as head of a research group, Dr. Friedmann frequently discussed his group's projects and capabilities with the heads of other research groups at UCSD, and vice versa. Based on these interactions, and the existing collaboration between the Friedmann and Lee groups to characterize the Rb gene structure, it was clear to Drs. Friedmann and Yee that Dr. Lee's group did not at that time have the expertise or experience in designing and constructing gene transfer vectors necessary for transfecting cancer cells with the Rb gene. (*See* Exhibit 1 at ¶ 4; Exhibit 2 at ¶ 4.) It was apparent to them that Dr. Lee's group sought the assistance of Dr. Friedmann's group in designing and constructing an efficient and effective vector for Rb because of the well-known expertise of the Friedmann lab in the area of retroviral mediated gene transfer. (*See* Exhibit 1 at ¶ 4; Exhibit 2 at ¶ 4.)

Of the members of Dr. Friedmann's research group at that time, Dr. Yee was most proficient at designing vector constructs. Consequently, he was assigned primary responsibility for conceiving of a design for and constructing the Rb vector. As was customary, Dr. Yee frequently reported to and consulted with Dr. Friedmann about Dr. Yee's progress while working on this project, and he made suitable changes in their strategy as needed based on their discussions. Dr. Yee was the member of Dr. Friedmann's research group who was most involved with the group's efforts to construct a vector for Rb, and who had the most interaction with members of Dr. Lee's group on this project. (*See* Exhibit 1 at ¶ 5; Exhibit 2 at ¶ 5.)

At the outset of the collaboration between Dr. Friedmann's group and Dr. Lee's group on the Rb vector project, Dr. Friedmann and Dr. Yee consulted on a strategy for designing a vector for Rb, and jointly conceived of a plan to modify their proprietary pLLRNL retroviral vector for this purpose. The pLLRNL vector was a retroviral vector that had been designed and constructed entirely in Dr. Friedmann's lab by members of his research team prior to any collaboration with Dr. Lee's group. At the time the Friedmann group collaborated with Dr. Lee's group, pLLRNL had not yet been disclosed in any published papers, and therefore it was considered proprietary to Dr. Friedmann's lab. (*See* Exhibit 1 at ¶ 6; Exhibit 2 at ¶ 6.)

In conceiving of a design for and constructing the Rb vector, Dr. Yee's primary concern was to construct a vector capable of stable and efficient transgene expression. There are a number of factors that influence proviral stability in any given case, all of which must be taken into consideration in designing the vector. These include: vector design, the nature of the reporter and selectable marker genes, the existence of internal transcription units, the nature of the internal promoter, the presence or absence of selective pressure, and the nature of the target cell. At the time of the Rb vector project, in the late Summer-Fall of 1987, there were no universally accepted rules available to the Friedmann group or any other research group for the design of stable and efficiently expressing vectors. Because Dr. Friedmann's laboratory was studying these factors far more actively than other laboratories, the Friedmann lab had a greater understanding of the importance of these factors than other investigators. In particular, Friedmann's group realized that each specific vector needs to be custom designed and tailored for the specific gene and target cell, and they had the requisite technical expertise to custom

design and construct such vectors. Dr. Friedmann's lab published its analysis of the various factors influencing vector design in 1989, after the establishment of the collaboration with Dr. Lee for the Rb vector preparation. (*See* Exhibit 1 at ¶ 7; Exhibit 2 at ¶ 7.)

The efforts of Dr. Friedmann's group resulted in the conception of and construction of a novel vector, pLRbRNL, which contained the Rb gene. Excerpts from Dr. Yee's lab notebook show in detail how he constructed the pLRbRNL vector. Based on his previous experiences with the proprietary pLRRNL vector, Dr. Yee concluded that placing the transgene under the control of the 5' LTR and the use of the RSV promoter as an internal promoter to drive the Neo gene expression seemed to be an optimal design. Although other arrangements of the vector components were possible, Dr. Yee selected the final version based on ongoing studies in his group of how retroviral vector design influences transgene stability and expression. Specifically, he knew from those studies that some of the arrangements resulted in unstable constructs or insufficient levels of expression, and that not only the nature of the gene but also the precise arrangement of the vector components can greatly effect long-term stability and expression. (*See* Exhibit 1 at ¶ 8; Exhibit 2 at ¶ 8.)

After Dr. Friedmann's group conceived of and constructed the pLRbRNL vector, they provided it to Dr. Lee's group to test in cancer cells. Using the same pLRbRNL vector that Drs. Yee and Friedmann had conceived of and constructed for them, Dr. Lee's group successfully introduced the cloned Rb gene into retinoblastoma and osteosarcoma cells that had inactivated endogenous Rb genes, and showed that expression of the exogenous Rb gene affected cell

morphology, growth rate, soft agar colony formation, and tumorigenicity. This is believed to be the first ever demonstration of suppression of the neoplastic phenotype by a single gene, and the findings were the subject of a paper published in the journal *Science* on December 16, 1988, on which Dr. Yee is listed as an author along with Dr. Friedmann and members of Dr. Lee's group. (*See* Exhibit 1 at ¶ 9; Exhibit 2 at ¶ 9.) A copy of that paper is attached as Exhibit 3.

The contents of that paper, including the details concerning the Friedmann group's conception of the design for and construction of the pLRbRNL vector, were subsequently incorporated substantially *verbatim* into U.S. Serial No. 265,829 ("the `829 application"), which was filed on October 31, 1988 (prior to the publication of the *Science* paper), on behalf of The Regents of the University of California and naming as inventors Dr. Wen-Hwa Lee and certain other members of his group. Neither Dr. Friedmann nor Dr. Yee were consulted regarding the preparation or filing of the patent application, nor were they listed as inventors. In fact, they were never told by Dr. Lee of the filing of this application, and only became aware of it much later in conversations with representatives of the University of California. (*See* Exhibit 1 at ¶ 10; Exhibit 2 at ¶ 10.)

Although the `829 application was filed on October 31, 1988, a patent did not issue from the `829 application until January 12, 1999, when U.S. Patent No. 5,858,771 issued to the Regents of the University of California. (*See* Exhibit 4, attached.) The `771 patent issued from U.S. Application Serial No. 337,855, which was a continuation of Serial No. 764,714, filed September 24, 1991, which in turn was a continuation of the `829 application.

It was not until 2000, when Dr. Friedmann and Dr. Yee decided that it was necessary to retain their own counsel, that they were able to conclude, with their counsel's aid, that an error in inventorship had occurred due to the fact that they were not named as coinventors of the originally filed application, i.e. the '829 application. (*See* Exhibit 1 at ¶ 11; Exhibit 2 at ¶ 11.)

2. Prosecution of the '855 Application

The disclosure, including claims, of the application filed herewith is identical to that of the `855 application as filed. As discussed above, the `855 application was a continuation of Serial No. 764,714, filed September 24, 1991, which in turn was a continuation of the `829 application. Accordingly, the specification of the present application is necessarily identical to the `829 application.

The portions of the *Science* paper that were incorporated into the `829 application can be found in columns 28-33 of the `771 patent, and the corresponding pages of the present application. (*Compare* Exhibit 3, attached, to columns 28-33 of Exhibit 4, attached.) The majority of the claims of the `855 application as filed were directed either to methods of controlling cancer suppression by gene therapy of a cancer suppressing gene or animals genetically altered as such. In an Office Action dated March 8, 1995, the USPTO rejected these claims under 35 U.S.C. § 112, first paragraph, as lacking enablement on the ground that

methods of gene therapy were considered experimental and highly unpredictable at that time. (*See* Prosecution History of U.S. Patent No. 5,858,771, Serial No. 337,855, Paper No. 3 (Exhibit 5, attached.)) To overcome this rejection, the University of California relied heavily on the data in the application that was taken directly from the *Science* paper. The University of California said in its response, *inter alia*:

> Applicants have demonstrated both *in vitro* and *ex vivo* that the instant methods and compositions indeed suppress the neoplastic phenotype. *Thus, retroviral vectors, containing the human RB gene effectively suppressed the neoplastic phenotype in vitro of human retinoblastoma* (WERI-Rb 27) and osteosarcoma (SAOS-2) cell lines lacking endogenous wild-type RB protein (see, for example, pages 75 through 85 of the specification).
> Furthermore, the introduction of a vector containing wild-type RB DNA into retinoblastoma cancer cells which, in turn, were implanted into nude mice, resulted in the suppression of the neoplastic phenotype of the implanted cells. This study in nude mice is set forth at pages 86 through 88 in the Specification. . . . *Thus, the Specification sets forth in clear and concise terms a method sufficient to enable the ordinarily skilled artisan to administer the RB gene in a vector to treat cancer* by suppressing the neoplastic phenotype of cancer cells lacking the wild-type RB protein.

(Prosecution History of U.S. Patent No. 5,858,771, Serial No. 337,855, Paper No. 6 at 9-10 (Exhibit 6, attached.)) (emphasis added.) In subsequently withdrawing the rejection, the Examiner indicated that the applicants' arguments had been pivotal: "The objection to the specification and the rejection of claims 1-14 under 35 U.S.C. § 112, first paragraph, . . . are withdrawn in view of Applicants' amendments to the claims and arguments in the Amendment . . . ." (Prosecution History of U.S. Patent No. 5,858,771, Serial No. 337,855, Paper No. 11 at 2 (Exhibit 7, attached.)) Although the Examiner later reinstated the rejection of the gene therapy claims on the ground that the application was enabling only for *in vitro* methods of treating mammalian cancer cells but not *in vivo* methods, it is clear that both the University of California and the USPTO

considered the concepts provided and work done by Drs. Yee and Friedmann to be central to the issue of enablement of the gene therapy claims. It is also clear that the claims would not have been allowed at that point without the conceptions of Drs. Friedmann and Yee.

3. The NCI Grant Application Filed by Dr. Lee in February 1989

Even after the publication of the *Science* paper, Dr. Lee continued to rely on the Friedmann group's expertise in designing and constructing Rb vectors. In February of 1989, shortly after the publication of the *Science* paper and the filing of the '829 application, Dr. Wen-Hwa Lee submitted a grant application on behalf of The Regents of the University of California to the National Cancer Institute in Bethesda, Maryland. The grant application was entitled "Mechanisms of cancer suppression by the human retinoblastoma gene." In it, Dr. Lee made numerous statements concerning the nature of the collaborations between his lab and Dr. Friedmann's lab, and the level of vector design expertise and technical ability of Drs. Friedmann and Yee.

For example, the grant application stated that Dr. Friedmann would be the Principal Investigator of the research unit responsible for developing vectors to deliver the Rb1 and Rb2 genes to tumor cells. In particular, Dr. Lee states:

> Ted Friedmann and Jiing-Kuan Yee will focus a major effort to developing a more efficient system for the reintroduction of RB genes into mammalian cells. *A considerable collaborative effort between the Lees [sic] and Friedmann groups resulted*

> *in the construction of the RB vector pLRbRNL with demonstrated tumor suppression capabilities.*

(*See* Exhibit 8, attached.) (emphasis added). Dr. Lee identified the responsibilities charged to the Friedmann unit as follows:

> The specific aims of this unit is [sic] to carry on these studies to: 1) modify the existing Moloney murine leukemia virus (MoMLV)-based vector LrbRNL for higher viral titres and RB gene expression; 2) develop more efficient retroviral vectors than the MoMLV-based vector; 3) determine long term effects of restoration of the RB gene product; 4) develop other in vivo gene delivery vehicles such as adeno-associated virus or liposome mediated gene transfer.

(*See* Exhibit 8, attached.) In touting the strength of his grant application, Dr. Lee specifically mentioned Dr. Friedmann and his researchers:

> Ted Friedmann has made significant contributions to the fields of virology and retroviral vectors for gene expression. . . . *Few groups in the world can match the Friedmann group's expertise and success in retroviral mediated gene transfer.*

(*See* Exhibit 9, attached.) (emphasis added.)

C. The State of the Retroviral Vector Art at the Time of Conception

An article published in 1989 and coauthored by Drs. Yee and Friedmann (Xu, L. *et al.*, "Factors Affecting Long-Term Stability of Moloney Murine Leukemia Virus-Based Vectors," *Virology 171*:331-341 (1989), is an authoritative description of the state of the retroviral art at the time the Lee and Friedmann labs collaborated. (*See* Exhibit 10, attached.)

The paper presents the results of the examination of long-term functional and structural stability of retroviral vectors. The authors note that "while the use of retroviral or other viral vectors is attractive to achieve a directed change in mammalian cells to complement a genetic defect and correct a disease phenotype (*i.e.*, gene therapy), it is obviously important to demonstrate that the genetic modifications are stable and associated with long-term transgene expression." (Exhibit 10 at page 339). They point out, however, that "even in experienced hands, the efficiency of production of transgenic animals is low, and the final appearance of only a small percentage of animals stably expressing transgenes suggests that integration or expression in at least some of the target cells may be transient and unstable." (Exhibit 10 at page 331.) The authors then proceed to identify numerous factors that affect proviral stability, and ultimately conclude that there are no established guidelines at that time for designing stable and efficiently expressing retroviral vectors:

> On the basis of these studies, it is possible to identify a number of interacting variables that can exert important influences on proviral stability. These include vector design, the nature of the reporter and selectable genes, the existence of internal transcription units and the nature of the internal promoter, the presence or absence of selective pressure, and the nature of the target cell. *We have not yet been able to deduce from the composite effects of these variables any universally applicable rules for the design of stable and efficiently expressing vectors.*

(Exhibit 10 at page 339.) (emphasis added.) The paper thus shows that it would not have been possible in 1988 for someone to routinely reduce to practice a retroviral vector design for gene therapy, because there was no established "practice" at that time. This is especially the case with scientists such as Dr. Lee who were not skilled in the art of retroviral expression.

There simply were no general rules available that would predictably have succeeded in any particular cell type, with any particular transgene and for any particular phenotype that one wanted to alter.

IV. The Legal Principles Governing Joint Conception of a Claimed Method or Process

A. Joint Inventorship Generally

The patent statutes require that an application for patent be applied for jointly by all inventors. 35 U.S.C. § 116. Specifically, § 116 provides:

> When an invention is made by two or more persons jointly, they shall apply for a patent jointly and each make the required oath . . . .

35 U.S.C. § 116. A joint invention is the product of collaboration between two or more persons working together to solve the problem addressed. *See Burroughs Wellcome Co. v. Barr Labs. Inc.*, 32 USPQ2d 1915 (Fed. Cir. 1994). Section 116 provides that collaborators may be joint inventors even though "(1) they did not physically work together at the same time, (2) each did not make the same type or amount of contribution, or (3) each did not make a contribution to the subject matter of every claim of the patent." 35 U.S.C. § 116.

Conception is the touchstone of inventorship. *See Ethicon Inc. v. U.S. Surgical Corp.*, 45 USPQ2d 1545, 1548 (Fed. Cir. 1998); *Fina Oil & Chem. Co. v. Ewen*, 123 F.3d 1466, 1473 (Fed. Cir. 1997); *Burroughs Wellcome*, 32 USPQ2d at 1919; *Sewall v. Walters*, 30 USPQ2d 1356, 1359 (Fed. Cir. 1994). Thus, "[d]etermining 'inventorship' is nothing more than determining who conceived the subject matter at issue . . . . *Sewall*, 30 USPQ2d at 415.

Conception is defined as the formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is thereafter to be applied in practice. *See Ethicon*, 45 USPQ2d at 1548. The conception must include every feature of the subject matter sought to be patented. *See Sewall*, 30 USPQ2d at 415. Conception is complete, *i.e.* an idea is sufficiently definite and permanent, when only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation. *See Ethicon*, 45 USPQ2d at 1548; *Burroughs Wellcome*, 32 USPQ2d at 1919; *Sewall*, 21 F.3d at 411. In the case of joint inventorship, "each joint inventor must generally contribute to the conception of the invention." *Ethicon*, 45 USPQ2d at 1548. More specifically, each inventor needs to perform only part of the task which produces the invention. *Id.*

"The determination of whether a person is a joint inventor is fact specific, and no bright-line standard will suffice in every case." *Fina*, 123 F.3d at 1473. It is clear, however, that "[t]he basic exercise of the normal skill expected of one skilled in the art, without any inventive act, does not make one a joint inventor." *Id.* Thus, one who simply provides the

inventor with well-known principles or explains the state of the art without ever having "a firm and definite idea" of the claimed invention as a whole does not qualify as a joint inventor. *See Ethicon*, 45 USPQ2d at 1548; *Fina*, 123 F.3d at 1473. In essence, the case law dictates that "to be a joint inventor, an individual must make a contribution to the conception of the claimed invention that is not insignificant in quality when measured against the dimension of the full invention." *Fina*, 123 F.3d at 1473.

B. Conception of a Claimed Method or Process

The Federal Circuit's predecessor, the Court of Customs and Patent Appeals, has defined conception of an inventive process as follows:

> Conception of an inventive process involves *proof of mental possession of the steps of an operative process* and, if necessary, *of means to carry it out* to such a degree that nothing remains but routine skill for effectuation thereof. If after the claimed conception date extensive research was found necessary before achieving minimum satisfactory performance obviously the mental embodiment of that date was a mere hope or expectation, a statement of a problem, but not an inventive conception.

(*Meitzner and Oline v. Corte and Meyer*, 161 USPQ 599, 603 (CCPA 1969), quoting *Alpert v. Slatin*, 134 USPQ 296 (CCPA 1962) (emphasis added). (*See* Exhibits 11 and 12, attached.) The Federal Circuit recently endorsed this standard in *Hitzemann v. Rutter*, 58 USPQ2d 1161 (Fed. Cir. 2001), an interference case involving a method for producing a hepatitis B vaccine by means of genetically altered yeast. (*See* Exhibit 13, attached.) In

Hitzemann, the court acknowledged that the goal of Hitzemann's research plan was to express in yeast particulate HBsAg suitable for a vaccine, and did not dispute that he even had possession of all of the necessary DNA tools to achieve the result. (*Id.* at 1169.) However, the court noted that Hitzemann specifically claimed the result of a biological process (i.e., expression by the yeast of the surface antigen, followed by assembly of the antigen into particles), and that the claimed process had never before been achieved. *Id.* Citing *Meitzner* and *Alpert*, the court held that "[w]hen a research plan requires extensive research before an inventor can have a reasonable expectation that the limitations of the count will actually be met, complete conception has not occurred." *Id.*

V. Statement of Reasons Why Relief Should Be Granted

It has been the University of California's position that Dr. Lee alone conceived of the general concept of introducing the retinoblastoma gene into an osteosarcoma cell line using a vector, and that the contributions of Drs. Friedmann and Yee in designing the vector that was ultimately successful in achieving that objective constituted merely a noninventive reduction to practice of Dr. Lee's basic conception. In essence, it is UC's contention that Dr. Friedmann and Dr. Yee acted merely as a "pair of hands" for Dr. Lee in this regard.

As discussed in detail below, UC's position is legally incorrect. When viewed in the context of the above-described factual background, including the admissions of Dr. Lee himself and the state of the retroviral vector art at the time of the collaboration between the Lee and

Friedmann labs, the controlling legal principles for inventorship dictate that Dr. Yee and/or Dr. Friedmann are inventors of certain subject matter claimed in the above-captioned application.

A. Dr. Lee's Group Sought to Collaborate with Dr. Friedmann's Group Because of the Well-Known Expertise of the Friedmann Group in the Area of Retroviral Mediated Gene Transfer

The University of California has never disputed that the specific vector used by Dr. Lee's group to deliver the Rb gene to cancer cells and demonstrate for the first time ever suppression of the neoplastic phenotype by a single gene was conceived of and constructed entirely by Drs. Yee and Friedmann. Rather, it has been the University of California's position that Dr. Friedmann's and Dr. Yee's efforts in this regard did not amount to joint conception of the claimed methods of suppressing the neoplastic phenotype using the Rb gene. In essence, the University of California contends that Dr. Lee's group sought the assistance of Dr. Friedmann's group merely for convenience, so that the Lee group could focus on more important efforts, and that Drs. Friedmann and Yee acted merely as pairs of hands to carry out a routine task assigned to them by Dr. Lee.

In fact, there is substantial evidence that indicates that the contributions of Drs. Yee and Friedmann were far more significant. Specifically, the expertise of the Friedmann group in designing and constructing retroviral vectors as well as Dr. Lee's own public statements, indicate that the contributions of the Friedmann group were far from "routine." Indeed, Dr. Friedmann is considered to be one of the world's leading authorities on the concepts and techniques of human

gene therapy, as recognized by his recent appointment as Chair of the Recombinant DNA Advisory Committee of the National Institutes of Health, which is charged with evaluating all gene therapy protocols submitted to the Federal Government. Dr. Friedmann's reputation was already well-established in the late Summer and Fall of 1987, when the Lee and Friedmann groups collaborated on the Rb vector project. Moreover, Dr. Friedmann's research group at UCSD was considered to be one of the world's foremost groups in terms of expertise and success with retroviral mediated gene transfer techniques and its applications to human gene therapy. In fact, Dr. Lee publicly admitted this in the grant application that he filed shortly after the Lee and Friedmann groups jointly published the study first demonstrating suppression of the neoplastic phenotype in cancer cells to which the Rb gene had been delivered by the pLRbRNL vector:

> Ted Friedmann has made significant contributions to the fields of virology and retroviral vectors for gene expression. . . . *Few groups in the world can match the Friedmann group's expertise and success in retroviral mediated gene transfer.*

(*See* Exhibit 9, attached.) (emphasis added.) As the member of Dr. Friedmann's group most proficient at vector design and construction, Dr. Yee would have been considered an expert in that area too.

In contrast, Dr. Lee's group did not at that time have the expertise or experience in designing and constructing gene transfer vectors necessary for transfecting cancer cells with the Rb gene. (*See* Exhibit 1 at ¶ 4; Exhibit 2 at ¶ 4.) It was apparent to Drs. Yee and Friedmann that Dr. Lee's group sought the assistance of Dr. Friedmann's group in designing and constructing an efficient and effective vector for Rb because of the well-known expertise of the Friedmann lab in

the area of retroviral mediated gene transfer. (*See* Exhibit 1 at ¶ 4; Exhibit 2 at ¶ 4.) Moreover, as one of the world's leading research groups in terms of its expertise and success with retroviral mediated gene transfer techniques, the Friedmann group was not interested in devoting substantial time to performing routine tasks for other research groups. Clearly, Dr. Lee's group sought to collaborate with Dr. Friedmann's group not because these scientists were just a pair of hands, but because of the unique expertise and insight that the Friedmann group had in retroviral mediated gene transfer techniques, which Dr. Lee himself acknowledged , and which expertise and insight were lacking in Dr. Lee's own group.

B. The Complete Conception of the Design of the pLRbRNL Vector as Well as Its Construction Was Entirely the Result of the Efforts of Dr. Friedmann and Dr. Yee, with No Input from Dr. Lee's Group

It must be emphasized that the University of California has never disputed that the specific vector used by Dr. Lee's group to deliver the Rb gene to cancer cells and demonstrate for the first time ever suppression of the neoplastic phenotype by a single gene was conceived of and constructed entirely by Drs. Yee and Friedmann. Because Dr. Yee was the member of Dr. Friedmann's group who was most proficient at designing vector constructs, he was assigned primary responsibility for conceiving of a design for and constructing the Rb vector. As was customary, Dr. Yee frequently reported to and consulted with Dr. Friedmann about Dr. Yee's progress while working on this project, and he made suitable changes in their strategy as needed based on their discussions. Dr. Yee was also the member of Dr. Friedmann's research group who was most involved with the group's efforts to construct a vector for Rb, and who had the most

the area of retroviral mediated gene transfer. (*See* Exhibit 1 at ¶ 4; Exhibit 2 at ¶ 4.) Moreover, as one of the world's leading research groups in terms of its expertise and success with retroviral mediated gene transfer techniques, the Friedmann group was not interested in devoting substantial time to performing routine tasks for other research groups. Clearly, Dr. Lee's group sought to collaborate with Dr. Friedmann's group not because these scientists were just a pair of hands, but because of the unique expertise and insight that the Friedmann group had in retroviral mediated gene transfer techniques, which Dr. Lee himself acknowledged , and which expertise and insight were lacking in Dr. Lee's own group.

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interaction with members of Dr. Lee's group on this project. (*See* Exhibit 1 at ¶ 5; Exhibit 2 at ¶ 5.) Therefore, he is in the best position to comment on the amount of guidance and input received from Dr. Lee's group.

Drs. Yee and Friedmann have both stated, in signed Declarations, that they consulted with each other at the outset of the collaboration on a strategy for designing a vector for Rb, and jointly conceived of a plan to modify their proprietary pLLRNL retroviral vector for this purpose. The pLLRNL vector was a retroviral vector that had been designed and constructed entirely in Dr. Friedmann's lab by members of his research team prior to any collaboration with Dr. Lee's group. At the time the Friedmann group collaborated with Dr. Lee's group, pLLRNL had not yet been disclosed in any published papers, and therefore it was considered proprietary to Dr. Friedmann's lab. (*See* Exhibit 1 at ¶ 6; Exhibit 2 at ¶ 6.)

In conceiving of a design for and constructing the Rb vector, Dr. Yee's primary concern was to construct a vector capable of stable and efficient transgene expression. The efforts of Drs. Yee and Friedmann resulted in the conception of and construction of a novel vector, pLRbRNL, which contained the Rb gene. Dr. Yee has submitted excerpts from his own lab notebook showing in detail how he constructed the pLRbRNL vector. Based on his previous experiences with the proprietary pLRRNL vector, Dr. Yee concluded that placing the transgene under the control of the 5' LTR and the use of the RSV promoter as an internal promoter to drive the Neo gene expression seemed to be an optimal design. Dr. Lee's group provided absolutely no guidance or instruction whatsoever regarding the design of the pLRbRNL vector. The pLRbRNL vector was

the vector used by Dr. Lee's group to deliver the Rb gene to cancer cells and demonstrate, for the first time, suppression of the neoplastic phenotype by a single gene.

C. The Conception of and Construction of the pLRbRNL Vector Was a Critical Contribution to the Conception of the Claimed Methods for Suppressing the Neoplastic Phenotype by Administration of the Rb Gene

1. At the Time that the Lee and Friedmann Groups Collaborated on the Rb Vector Project, There Were No Universally Accepted Rules Governing the Design of Stable and Efficiently Expressing Retroviral Vectors

As one of the world's foremost authorities on human gene therapy, Dr. Friedmann is qualified to discuss the state of the art of retroviral mediated gene transfer techniques and its applications to human gene therapy as it was in late Summer - Fall of 1987. Indeed, the paper that he coauthored with Dr. Yee and others entitled "Factors Affecting Long-Term Stability of Moloney Murine Leukemia Virus-Based Vectors" (*Virology 171*:331-341 (1989)) is particularly relevant in this regard.

There are a number of factors that influence proviral stability in any given case, all of which must be taken into consideration in designing the vector. These include: vector design, the nature of the reporter and selectable marker genes, the existence of internal transcription units, the nature of the internal promoter, the presence or absence of selective pressure, and

the nature of the target cell. At the time of the Rb vector project, in the late Summer-Fall of 1987, there were no universally accepted rules available to the Friedmann group or any other research group for the design of stable and efficiently expressing vectors. Because Dr. Friedmann's laboratory was studying these factors far more actively than other laboratories, the Friedmann lab had a greater understanding of the importance of these factors than other investigators. In particular, Friedmann's group realized that each specific vector needs to be custom designed and tailored for the specific gene and target cell, and they had the requisite technical expertise to custom design and construct such vectors. Dr. Friedmann's lab published its analysis of the various factors influencing vector design in 1989, after the establishment of the collaboration with Dr. Lee for the Rb vector preparation. (*See* Exhibit 1 at ¶ 7; Exhibit 2 at ¶ 7.)

The efforts of Dr. Friedmann's group resulted in the conception of and construction of a novel vector, pLRbRNL, which contained the Rb gene. Based on their previous experiences with the proprietary pLRRNL vector, Dr. Yee concluded that placing the transgene under the control of the 5' LTR and the use of the RSV promoter as an internal promoter to drive the Neo gene expression seemed to be an optimal design. Although other arrangements of the vector components were possible, Dr. Yee selected the final version based on ongoing studies in his group of how retroviral vector design influences transgene stability and expression. Specifically, he knew from those studies that some of the arrangements resulted in unstable constructs or insufficient levels of expression, and that not only the nature of the gene but also

the precise arrangement of the vector components can greatly effect long-term stability and expression. (*See* Exhibit 1 at ¶ 8; Exhibit 2 at ¶ 8.)

Thus, it is clear that Drs. Yee and Friedmann provided critical expertise and insight in designing and constructing the pLRbRNL vector that was ultimately used by the Lee group to deliver the Rb gene to cancer cells and demonstrate, for the first time ever, the suppression of the neoplastic phenotype by a single gene.

2. *Dr. Lee Has Publicly Admitted the Expertise of the Friedmann Group in Retroviral Mediated Gene Transfer and that The Contribution of the Friedmann Group to the Design of the pLRbRNL Vector Was "Considerable"*

In the grant application filed by Dr. Lee with the National Cancer Institute in Bethesda, Maryland, Dr. Lee indicated that Dr. Friedmann would have considerable responsibilities as Primary Investigator of the unit charged with further developing vectors for delivering the Rb gene to tumor cells. In particular, Dr. Lee stated:

> The specific aims of this unit is [sic] to carry on these studies to: 1) modify the existing Moloney murine leukemia virus (MoMLV)-based vector LrbRNL for higher viral titres and RB gene expression; 2) develop more efficient retroviral vectors than the MoMLV-based vector; 3) determine long term effects of restoration of the RB gene product; 4) develop other in vivo gene delivery vehicles such as adeno-associated virus or liposome mediated gene transfer.

(*See* Exhibit 8, attached.) In addition, Dr. Lee indicated that the contributions of the Friedmann group to the Rb vector project were significant:

> Ted Friedmann and Jiing-Kuan Yee will focus a major effort to developing a more efficient system for the reintroduction of RB genes into mammalian cells. *A considerable collaborative effort between the Lees and Friedmann groups resulted in the construction of the RB vector pLRbRNL with demonstrated tumor suppression capabilities.*

(*See* Exhibit 8, attached.) (emphasis added).

It is evident that Dr. Lee greatly valued the expertise of the Friedmann group in the area of retroviral mediated gene transfer techniques and its applications to human gene therapy, as evidenced by his continued reliance on the Friedmann group to further develop Rb vectors. It is also evident that Dr. Lee considered the contribution of the Friedmann group to the initial Rb vector project to be far from insignificant. Indeed, Dr. Lee did not at that time, when he was attempting to obtain funding from the U. S. Government, consider Drs. Friedmann and Yee to be just one more source of possible Rb vectors. Quite the contrary, Dr. Lee specifically touted the expertise and reputation of the Friedmann lab to convince the U. S. Government to finance his research. It is only now, after the fact, that Dr. Lee and his assignee, The Regents of the University of California, seem to take the position that Drs. Yee and Friedmann merely served as a "pair of hands."

C. *Until Dr. Yee and Dr. Friedmann Conceived of A Specific Vector Capable of Delivering the Rb Gene to Cancer Cells, Conception of the Claimed Methods of Suppressing the Neoplastic Phenotype Was Incomplete and, Therefore, Not Enabled*

The Federal Circuit's predecessor, the Court of Customs and Patent Appeals, has defined conception of an inventive process as follows:

> Conception of an inventive process involves *proof of mental possession of the steps of an operative process* and, if necessary, ***of means to carry it out*** to such a degree that nothing remains but routine skill for effectuation thereof. If after the claimed conception date extensive research was found necessary before achieving minimum satisfactory performance obviously the mental embodiment of that date was a mere hope or expectation, a statement of a problem, but not an inventive conception.

(*Meitzner and Oline v. Corte and Meyer*, 161 USPQ 599, 603 (CCPA 1969), quoting *Alpert v. Slatin*, 134 USPQ 296 (CCPA 1962) (emphasis added). The Federal Circuit recently endorsed this standard in *Hitzemann v. Rutter*, 58 USPQ2d 1161 (Fed. Cir. 2001).

It is clear that at the time Dr. Lee's group sought to collaborate with Dr. Friedmann's group on the Rb vector project, Dr. Lee, at the very least, did not have "the means to carry out" his wish of providing expression of the Rb gene in osteosarcoma cells, and had no idea whether or not such expression would suppress the neoplastic phenotype.

Based on the above cases, it is clear that at the time Dr. Lee approached Dr. Friedmann's lab and asked for their help in designing a vector for introducing the Rb gene into osteosarcoma cells, Dr. Lee had no more than a wish or hope to achieve tumor suppression by

gene therapy, but he did not have a conception of a complete and operative method for accomplishing it. Dr. Lee provided Dr. Friedmann's lab with no means for how to introduce the gene into the cells. Moreover, Dr. Lee could not have reasonably expected that he would be capable of suppressing the neoplastic phenotype in the cells by introduction of a single tumor suppressor gene such as retinoblastoma, because that had never before been accomplished in the art.

Moreover, during prosecution of the '771 patent, the applicants specifically relied on the success of the vectors designed by Friedmann and Yee to overcome rejections based on lack of enablement due to unpredictability in the gene therapy art. In an Office Action dated March 8, 1995, the USPTO rejected the claims under 35 U.S.C. § 112, first paragraph, as lacking enablement on the ground that methods of gene therapy were considered experimental and highly unpredictable at that time. To overcome this rejection, the University of California relied heavily on the data in the application that was taken directly from the *Science* paper. The University of California said in its response, *inter alia*:

> Applicants have demonstrated both *in vitro* and *ex vivo* that the instant methods and compositions indeed suppress the neoplastic phenotype. *Thus, retroviral vectors, containing the human RB gene effectively suppressed the neoplastic phenotype in vitro of human retinoblastoma* (WERI-Rb 27) and osteosarcoma (SAOS-2) cell lines lacking endogenous wild-type RB protein (see, for example, pages 75 through 85 of the specification).
> Furthermore, the introduction of a vector containing wild-type RB DNA into retinoblastoma cancer cells which, in turn, were implanted into nude mice, resulted in the suppression of the neoplastic phenotype of the implanted cells. This study in nude mice is set forth at pages 86 through 88 in the Specification.... *Thus, the Specification sets forth in clear and concise terms a method sufficient to enable the ordinarily skilled artisan to administer the RB gene in a vector to*

> *treat cancer* by suppressing the neoplastic phenotype of cancer cells lacking the wild-type RB protein.

(*See* Exhibit 6, attached.)) (emphasis added.) In subsequently withdrawing the rejection, the Examiner indicated that the applicants' arguments had been pivotal: ("The objection to the specification and the rejection of claims 1-14 under 35 U.S.C. § 112, first paragraph, . . . are withdrawn in view of Applicants' amendments to the claims and arguments in the Amendment . . . .") (*See* Exhibit 7, attached.)

Dr. Lee then, not only used his association with the Friedmann lab to obtain funding from the U.S. Government, but he also used the Yee/Friedmann conception of the vector to convince the USPTO that his claims to gene therapy were enabled. Apparently, Dr. Lee and his assignee, The Regents of the University of California, were quite willing to use the reputation and accomplishments of, and collaboration with, the Friedmann lab where necessary to further their own interests before the National Cancer Institute or the USPTO. However, they failed to correctly name these crucial collaborators as coinventors when they filed their patent application.

In view of the above, it is clear that the identification of a *specific* vector capable of stably and efficiently introducing the Rb gene into cancer cells and with a demonstrated ability to suppress the neoplastic phenotype was *essential* to enablement of the claimed methods for gene therapy. Thus, prior to conception of the pLRbRNL vector, the first vector ever to accomplish this, the claimed objective of methods of gene therapy where merely a hope or wish, but not a complete and operative conception of the claimed invention. Indeed, the

USPTO would have never dropped the rejection under 35 U.S.C. § 112, first paragraph, had it not been for the critical conceptions and contributions of Drs. Friedmann and Yee.

VI. Conclusion

It is respectfully submitted that the evidence, taken as a whole, shows very clearly that an error in inventorship exists with respect to the above-captioned application. Accordingly, it is requested that the Examiner either (1) make a formal statement that the inventorship of the above-captioned application as filed is improper, and that Dr. Yee and/or Dr. Friedmann should be added as inventors; or (2) reject one or more claims under 35 U.S.C. § 102(f) on the ground of derivation due to the fact that Dr. Yee and/or Dr. Friedmann are coinventors of the subject matter of one or more claims of the above-captioned application yet have not been listed as inventors.

Respectfully submitted,

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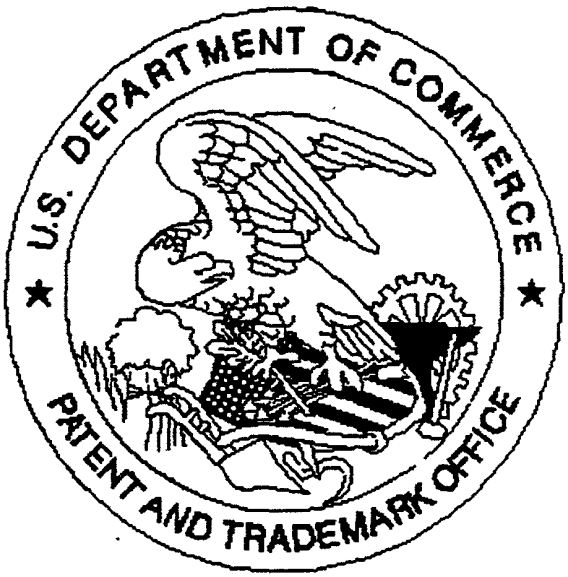

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